Outcome assessment and economic evaluation of short-stay intensive care for coronary artery bypass patients

CHAPTER

Summary and general discussion

This chapter contains six major parts, which will summarize and discuss the contents of this thesis. In the first part (1) a summary will be given of the different studies performed. The barriers for implementation of the short-stay intensive care intervention will be discussed in the second part (2). In the third part (3) aspects of framing future research will be discussed. In the fourth part (4) the use of different quality of life measures for future research will be discussed. In the fifth part (5) the impact of using adjustment methods to correct imbalances in baseline utility in QALY calculations on the SSIC study findings will be discussed. In the last two parts (6 and 7) a summary of recommendations for future research will be given.

1 Summary

1.1 State of the art of fast-track treatments for low-risk CABG patients (chapter 2)

In the second chapter the results of a systematic review are described. None of the previous studies that evaluated fast-track treatments focussed on IC discharge criteria. They investigated related topics as type and dose of anesthetics (high dose: fentanyl>15µg/kg, low dose: fentanyl<15µg/kg) or extubation protocols used (the intention to extubate patients within or after 8 hours postoperative). 27 randomised controlled trials evaluating fast-track treatments were identified. The main finding of this review and meta–regression analysis is that the introduction of an early extubation protocol is an important predictor for the decrease of IC and total hospital stay in low-risk CABG patients.

The epidemiological quality of the studies was moderate. Only one study fulfilled all three methodological criteria: the use of intention-to-treat analysis for the primary study outcome IC stay, allocation concealment (is patient really randomly assigned to one of the treatment arms) and blinding of person(s) deciding on the length of IC stay.

The quality of the economic evaluations (EEs) of the 7 studies reporting on costs was assessed by means of the Consensus Health Economics Criteria list (CHEC-list). The CHEC-list scores on the 17 evaluated items of the various studies were low (on average 8 points). The drawbacks of these studies were mainly related to the choice of study design (not appropriate to the stated objective) and costing methods (irrelevant costs were identified and not appropriately valuated). The findings of our review indicate that there is a need for quality improvement of both the study design and the design of EEs.

1.2 Clinical effectiveness and cost-effectiveness of the SSIC protocol (chapter 3)

The short-stay intervention is evaluated in low-risk CABG patients by means of a randomised controlled clinical equivalence trial and an EE performed alongside it. We defined low-risk patients as patients who fulfilled the following criteria: having a stable cardiological situation (not having a cardiogenic shock, no need for inotropic therapy, no need for intraaortic balloon pump, and no ongoing or recent myocardial infarction), age < 78 years, ejection fraction of > 30% and not requiring hemodialysis or having pulmonary hypertension. Patients assigned to the SSIC group were transferred from IC to MC within 8 hours if they fulfilled the following discharge criteria: extubated for at least 30 minutes, normal breathing, arterial blood gas pO_2 > 10 Kpa and PCO_2 < 6.0 Kpa, cardiac stable, fluid balance in control (≤ 100 ml chest tube drainage per hour and a diuresis > 0.5 ml/kg/hour), no signs/symptoms of neurological complications, no need for hemodynamic and supporting therapy.
The primary study endpoints were IC readmission and total hospital stay. IC readmission was 1.34% (*n*=4) and 2.68% (*n*=8) in the control group and the SSIC group respectively. The difference of 1.13% was not significantly different (P-value = 95% CI: -.9% to 2.9%). No differences were found between the two groups with respect to 'total hospital stay' and the sec-

ondary outcomes measures 'postoperative morbidity' and '30 day-mortality'. The patients in the SSIC group spent significantly fewer hours at the IC compared to control group patients. In the intervention group the mean costs per patient were €4,625 versus €5,441 in the control group. The difference was €-816, mainly due to lower costs of clinical procedures and IC stay. The generic quality of life was valuated by societal health values. The delta quality adjusted life months (Δ QALM) was significantly different between the two groups, in favour of the SSIC group. The incremental cost-effectiveness ratio and 98% of the bootstrapped ICERs were situated in the Southeast quadrant, indicating that the SSIC group is dominant over the control group. The conclusion of this study is that SSIC is a safe and cost-effective approach compared to usual care.

1.3 Health-related quality of life after fast-track treatment (chapter 4)

The objective of this prospective randomised equivalence trial was to evaluate disease specific (Multidimensional Index of Life Quality), generic (EQ-5D) and domain specific (Beck Depression Inventory, State-Trait Anxiety Inventory) health-related quality of life (QoL) until one year after fast-track treatment for low-risk coronary artery bypass patients (CABG patients). Quality of life was measured at baseline, one and twelve months after treatment. The main findings were that in a multivariate analysis at one year after surgery no statistically significant differences in QoL between the two groups were shown. In addition, after controlling for potential confounders at one year no statistical significance between both groups was found. The conclusion of this study is that QoL of SSIC patients are similar to patients receiving care as usual, and that none of the observed QoL differences between the two groups can be defined as clinically meaningful.

1.4 Testing validity and reliability of the EuroQoL and Multidimensional Index of Life Quality (chapter 5)

The objective of this prospective comparative study was to test the validity and reliability of the EuroQoL (EQ-5D) and the Multidimensional Index of Life Quality (MILQ, a disease specific instrument) in coronary artery bypass surgery patients.

The main findings of this comparative study were that the discriminative validity was limited due to substantial ceiling effects in all five EQ-5D dimensions shown. These effects were also observed in the MILQ dimensions financial status and healthcare professionals. The predictive validity at one month of the EQ-5D domain anxiety/depression, EQ-5D VAS, MILQ domain physical health and the MILQ-score was moderate. At 12 months after surgery the EQ-5D VAS, MILQ-score and the two physical dimensions of the MILQ had a good predictive validity. Only the EQ-5D domain usual activities and the EQ-5D VAS distinguished between patients of different New York Heart Association functional classification categories (external criterion validity). The test-retest reliability of both questionnaires can be classified as not adequate.

The conclusions of this study are that the discriminative validity of the EQ-5D domains, the external criterion and the predictive validity of both the EQ-5D and the MILQ were limited. In addition the reliability of both questionnaires was not adequate. These questionnaires are not the first choice when evaluating QoL in CABG patients.

1.5 Adjustment methods for imbalances in baseline utility between treatment groups in QALY calculations (chapter 6)

The objective of this study was to evaluate different strategies, which correct imbalances in baseline utility in quality adjusted life year (QALY) calculations and are suited for the analysis of data on a patient level.

The data of a trial based cost-effectiveness study evaluating a short-stay intensive care treatment for coronary artery bypass patients was used as

a case study. Five different methods were used for calculation of QALY differences: 1) Conventional QALY calculation method (no adjustment for imbalances in baseline utility); 2) Mean difference adjustment method: correction with the differences in the mean baseline utility of the treatment groups; 3) Delta adjustment: uses the change in utility over time; 4) Regression-based utility adjustment: adjusting the follow-up utility with a regression model with the follow-up utility as dependent variable, and baseline utility as independent variable; 5) Regression-based QALY adjustment: adjusting the QALY with a regression model with the QALY as dependent variable, and baseline utility as independent variable.

The results of this study show that not applying a correction method for the calculation of QALYs when imbalances in baseline utility occur, results in a different cost-effectiveness outcome compared to various simple or advanced correction methods for the calculation of QALYs having been applied. The magnitude of the impact of these correction methods on the study outcome is dependent on the type of correction method used. We recommend in case of imbalances in baseline utility to report the outcomes of the regression-based QALY adjustment in the base case analysis and to report the outcomes of the other proposed adjustment methods in additional sensitivity analyses.

2 Possibilities for implementation of the current SSIC protocol

The encouraging results of the SSIC study make it desirable to implement the SSIC protocol. We know that in the Netherlands hospitals use fast-track protocols; at the moment, however, more than three years after publication of the main study findings, we did not get any information about hospitals currently using our protocol.

One may ask if the findings of one randomised controlled trial and an EE performed alongside it are sufficient evidence to policy makers to actually decide to use the SSIC protocol in their hospitals? This study demonstrates the second-best level of evidence (level 1B): an individual ran-

domised controlled trial with narrow confidence intervals. In other words an randomised controlled trial which excludes clinical harm from the new treatment (Straus, 2005). The best level of evidence is not available as this was the first study that evaluated this type of fast-track treatment (SSIC-protocol) and therefore no systematic review with homogeneity of randomised controlled trials could be performed (Level 1A).

Reliability and transferability of the study findings will be discussed below as they are also important to decision makers in making decisions on whether or not to implement a new treatment strategy (Drummond & Pang, 2001; Mason & Mason, 2006). Decision makers need to be convinced of the reliability of the study findings, in other words; does the study give an accurate estimate of the study outcomes, which are free of biases? This may apply to the main effect measure of the EE, the QALY. Several surveys indicate that policymakers are less comfortable with the methods of QALY calculations. They find the concepts behind the measurements difficult to understand, they have concerns about the reliability of the estimation methods themselves, and finally, they have a general concern about the aggregation of healthcare benefits in a single index (Barbieri, 2005). The transferability of a study means, to which extent study findings of a specific study are directly applicable to the decision maker's own setting. This is not always the case with cost-effectiveness findings, as they can vary by settings, by levels of clinical experience, by disease severity, by co-morbidity, by resource use, by prices and by utilities (Manca, 2005; Mason & Mason, 2006; Sculpher, 2006). This may be a reason for decision makers not to implement the SSIC protocol. However, not implementing the protocol for transferability reasons was minimized by thoroughly and accurately describing the study design, conduct, and analysis in the published articles. By doing so, policy makers were able to distillate which part of the findings do or do not apply to their own specific healthcare setting.

An important step in the implementation process is to determine various potential barriers that impede implementation (Grol & Wensing, 2001). In the following sections the potential barriers of implementation of the SSIC protocol related to the system (infrastructure and budgets (2.1.1-2.1.2)) and the social environment (healthcare professionals and patients) will be discussed (2.1.3-2.1.4).

2.1.1 System: Infrastructure of the IC and MC

Cardio Thoracic (CT) ICs in the Netherlands can have different structures: being a separated CT IC, the CT unit is situated on the general IC, and a combined CT-cardiology IC. An MC care facility is not always available and therefore patients sometimes need to be directly transferred to the nursing ward. If centers do not have a separated CT IC nor a MC directly attached to the IC, this may pose a barrier to the implementation of the SSIC protocol, and, subsequently, to patient logistics.

2.1.2 System: Budgets

From a health economic point of view the available resources as a result of the reduced IC hours and clinical procedures can be used for the treatment of more complex patients. Another possibility of a more efficient use of IC and MC capacity can be that more surgeries can be performed and fewer patients are being refused for IC admission. However, although decision makers will understand these abovementioned arguments their main concern is the financial budget constraints. Currently the reimbursement per treated patient is not related to the total stay at the various departments, but to all aspects of a specific clinical pathway (DBC; Dutch for Diagnosis treatment Combination). Besides, another important aspect for not implementing the SSIC protocol will be the costs of the actual implementation of the intervention itself. These are for instance the costs of rebuilding the IC and/or MC departments and the costs of education and organizing meetings for healthcare professionals.

2.1.3 Social environment: healthcare professionals

Due to the fact that it is not possible to predict exactly at what time of the day which and how many SSIC patients will be ready to be transferred to medium care, the planning of personnel can be a barrier to healthcare professionals to implement the protocol. In our study 55% of the SSIC patients fulfilled the discharge criteria and were transferred from IC to MC within 8 hours. As the decision to transfer SSIC patients can be made not only at 8 hours but at any time a patient has a stable clinical situation (for instance at 6 or 12 hrs after surgery), these percentages will probably be higher in daily practice. Further research is needed to confirm these expectations.

Another barrier related to healthcare professionals can be the type of profession of the general manager of the IC department. He or she can decide whether or not to implement the SSIC protocol. For example, the development of the SSIC protocol by a cardiac surgeon might affect the acceptability for implementation by other professions, like intensivists or anesthesiologists who can also be the general managers of the IC.

Other potential barriers might be the attitude and resistance to change felt by IC and MC nursing staff. During the Maastricht trial e.g. nurses were very sceptical about the benefits of treating patients according to the SSIC protocol, as they feared that their workload would increase (for example, patients are not constantly asleep any more during their stay at the IC department).

2.1.4 Social environment: patients

The following data indicate that the motivation for implementing a SSIC protocol specially developed for low-risk CABG patients may have decreased in recent years due to changes in the CABG-patient population. From 2004 to 2006 a decline of the number of hospitalizations due to CABG and an increase of the number of hospital admissions for percutaneous coronary interventions (like stent placement) was observed in

the Netherlands (Prismant, 2008). A comparable trend was also observed in other western countries (Nallamothu, 2007). These results, together with ageing, resulted in a greater proportion of higher risk cardiac patients who were selected for elective surgery (Cheng & Barash, 2006; Flynn, 2004; Goss, 2006).

3 Framing a future study

As discussed, implementation of the SSIC protocol is difficult for various reasons. Therefore it is important that future studies in this field must diminish the implementation barriers by taking them into account as much as possible in the design phase of the study. The development of a new EE in this field will be discussed by means of the concept of framing. Framing can be defined as a series of decisions that collectively define and describe the EE study to be undertaken (Gold MR, 1996). The main aspects of framing are; defining the study objective and audience (3.1), the type of analysis (3.2), the perspective of the analysis (3.3), the intervention and the comparison treatment and the target population (3.4), and finally the boundaries and the time horizon (3.5).

3.1 Objective and audience

In our opinion the objective of a future study must be: performing a before-after multicenter trial with EE evaluating the entire clinical pathway of CABG patients. In the first 12 months before evaluating the clinical pathway, all relevant clinical outcomes, quality of life and cost data need to be gathered for the care as usual in various hospitals. In the second period of 12 months the same data will be collected when treating patients according to the clinical pathway.

The primary audience of this new study is the general managers of the IC units and the board of directors of the hospitals. Therefore it is important to focus the analysis on topics that are relevant for these two groups of decision makers. For instance, a future study should focus more on an

intervention that can easily be implemented in different hospital settings. Besides the costs and consequences that are part of a conventional EE, other aspects that are important to decision making should be assessed as well. Issues that need to be included are for example: calculations of the implementation costs, and scenario analyses on the impact of the new treatment on changes in patient flow and waiting lists.

3.2 Type of analysis

As it is expected that the clinical pathway of CABG patients is more effective compared to the usual care, the preferred type of analysis of a future study is CEA (or CUA). However, given the idea described above that other aspects are relevant to decision makers, the framework of cost-outcome analysis, being a specific method of EE, might be considered for this purpose to cover the outcomes that cannot be expressed as either costs or patient outcome.

3.3 Perspective of analysis

For a future study we would advise to choose both the hospital and societal perspective for the EE. A hospital perspective should be used, because at this level the decisions about the use of the clinical pathway of CABG patients will be made. A societal perspective is also important for the foundation of arguments for implementation. Due to the proposed changes in treatment it is expected that treatment according to the clinical pathway will have a positive effect on recovery (like reduced overall hospital stay, higher scores on physical aspects of quality of life) compared to care as usual. Patients treated according to the clinical pathway for instance will be discharged earlier from hospital after surgery. In addition, cost-savings will probably take place. The direct medical costs, like the hospital costs (costs of inpatient days and clinical procedures) will probably decrease, but some indirect medical costs will probably increase (for instance more informal care or paid help after

hospital discharge will be needed). The indirect non-medical costs, however, will be lower as it is expected that the intervention patients restart normal and daily life sooner (shorter absence from (volunteer) work) compared to patients who are not treated according to the new clinical pathway.

3.4 Defining the intervention, comparison treatment and target population

Details of the clinical pathway must be clearly specified in a future study. This means that not only the intervention on the different departments (IC, MC and ward) needs to be described in detail but also the care as usual. In the description of the IC protocol details of early extubation, frequencies of regular checks, temperature management, sedation and pain management are important. The difference between this future study and the performed SSIC study is that not only must it focus on the evaluation of an intervention in the first hours of intensive care treatment, but on all aspects of the pre-, peri- and postoperative care of CABG patients. An important aspect of this new study should be that patients who fulfill the IC discharge criteria are immediately transferred to a lower care facility (MC or ward). In addition not only discharge after 8 hours IC treatment must be considered as an option for transferring patients, but other time points in a range of 6 to 12 hours should also be included. These protocols must also describe details of, for instance, the preoperative screening day, temperature management during surgery, anesthetic doses, mobilization of patients by physiotherapist and nurses. As discussed in the implementation section the care as usual can vary between different hospitals and settings. It is important to compare, if possible, the new clinical pathway with the most important comparators of care, which are the most realistic policy choices.

The target population of a future study should contain both low-risk and high-risk CABG patients and the eligibility criteria need to be based on current standards of risk stratification (Michel, 2003; Nilsson, 2006).

3.5 Boundaries and time horizon of the economic evaluation

The scope of a future study should be the evaluation of the clinical effectiveness and cost-effectiveness of the clinical pathway for all CABG patients. Aspects that are not primarily related to the abovementioned scope, like the influences on quality of life of family members and costs made by those relatives due to illness of the patients under study, should not be incorporated in the analysis.
In a future study the follow-up must be until one year after treatment, for all relevant study outcomes: clinical outcomes, quality of life and costs. One year follow-up can be chosen as the time frame for this study as it is a well accepted follow-up for rehabilitation after CABG surgery (Badia, 2001; Borkon, 2002; Cheng & Barash, 2006).

4 Choosing quality of life measures for a future study

4.1 Generic quality of life measures

In many ways it is important to know the possible effects of a new treatment on quality of life. One of its merits is that it can help clinicians to explain to patients what they can expect from a specific treatment. Besides, if more than one therapeutic option is available, this knowledge -in addition too clinical and cost-effectiveness- contributes to making rational choices concerning the most appropriate therapy. As the measurement of QoL is subjective it is very important to use validated and reliable instruments. The EQ-5D was chosen in the SSIC study as generic measure for several reasons. Firstly, it is has good psychometric proportions (Brazier, 1993). Secondly, it is brief, simple and easy to administer (only 6 items). In addition it is suitable for EE as it can generate a single index score for health (utility) by means of population weights (Dolan, 1997). Besides using it for the EE (chapter 3) we wanted to use the same instrument for describing patients' quality of life in the five different dimensions, so we could use this in the QoL-study (chapter 4).

Based on our findings of the validity and reliability study (chapter 5) it may be better not to choose the EQ-5D but another generic instrument for the evaluation of QoL in evaluation study of the clinical pathway for CABG patients. There are several other preference-based measures that can be considered. The other questionnaires most commonly used with the same possibilities as the EQ-5D are the Short Form-36 (SF-36) and the Health Utilities Index (HUI). The HUI contains 15 questions and classifies patients in either HUI2 or HUI3 health states. In our opinion this questionnaire contains attributes that are not relevant for the evaluation of the clinical pathway: sensation and fertility in the HUI2; vision, hearing, speech and fertility in the HUI3.

Should we then use the SF-36 (and therefore the SF-6D) for a future study instead of EQ-5D? A theoretical advantage of the SF-6D is that it contains a larger descriptive system (i.e. 18.000 unique health states can be described by SF-6D compared to only 243 by EQ-5D), therefore it potentially has greater ability to identify small changes (Bryan & Longworth, 2005). Another advantage of using the SF-6D is its better ability to detect improvements in the upper range of the utility scale in cardiovascular disorders (Moock & Kohlmann, 2008). A disadvantage of the SF-6D is that it does not describe health states at the lower end of the scale (Longworth & Bryan, 2003). Based on a head-to-head comparison of EQ-5D and SF-6D in patients with coronary heart disease Van Stel concluded there is no clear benefit of using SF-6D in clinical studies instead of EQ-5D (van Stel & Buskens, 2006). Others do not prefer one to the other (Kopec & Willison, 2003) either as both questionnaires have several disadvantages. Some authors found no sensitivity to change of SF-6D after the intervention (Longworth & Bryan, 2003; Smith, 2000; van Stel & Buskens, 2006). We were also not able to demonstrate sensitivity to change for EQ-5D (chapter 5). In our opinion based on the above-mentioned advantages and disadvantages and the results of our study (chapter 5) either SF-6D or EQ-5D

should be chosen for the measurement of generic quality of life in a future study evaluating the entire clinical pathway for CABG patients.

4.2 Disease specific quality of life measures

For the assessment of QoL of people with ischemic heart disease it is recommended to use a disease specific QoL questionnaire (Dempster & Donnelly, 2000) in addition to a generic questionnaire. In the QoL-study (chapter 4) we used the Multidimensional index of quality of life (MILQ) as disease specific instrument. There were two reasons why we chose this questionnaire in our evaluation study: a Dutch version of this questionnaire was already available, and both psychometric proportions (validity and reliability) were extensively examined by Avis et al. (Avis, 1996). The conclusion of these authors was that this instrument was valid and reliable, contrary to our study findings (chapter 5).

At the moment there are various other options for the evaluation of disease specific QoL of the clinical pathway of CABG patients. The two most commonly used are the Seattle Angina Questionnaire (SAQ) (Dougherty, 1998; Spertus, 1995) and the MacNew Heart Disease Questionnaire (MacNew) (Lim, 1993). The SAQ consists of 19 items, which are grouped in five separate domains: physical limitation, angina stability, angina frequency, treatment satisfaction and disease perception. The MacNew consists of 27 items, which fall into the following three domains: physical limitations, emotional function and social function. All domains of the MacNew and SAQ are responsive and their test-retest reliability can also be classified as high (Dougherty, 1998; Hofer, 2003; Hofer, 2004; Spertus, 1994; Spertus, 1995). Furthermore, it was found that none of the SAQ domains and most of the MacNew domains are able to discriminate between patients in Canadian Cardiovascular Society functional classes I-IV (Hofer, 2003). Dougherty et al., however, found that all the SAQ domains except for treatment satisfaction were able to discriminate between Canadian Cardiovascular Society functional classes I–III. Based on previous

findings we can conclude that the psychometric proportions of both questionnaires can be classified as good. However, none of the SAQ and only a few of the studies evaluating the reliability and validity of the MacNew are performed in the Netherlands. In addition to this the study population consisted mostly of patients with a stable angina and not of a population of CABG patients. Therefore in our opinion further research is needed to either prefer the SAQ to the MacNew for the measurement of disease specific QoL in a future study evaluating the clinical pathway for CABG patients.

5 Effects of using correction methods for imbalances in baseline utility in QALY-calculations on SSIC study findings

In our EE (chapter 2) we corrected for imbalances in baseline utility by means of the delta method. The conclusion of the EE based on using this correction method was that the SSIC was a cost-effective treatment. Although this correction method is generally accepted (Cheng, 2000; Guthrie, 1999; Hurskainen, 2001; Lee, 2002; Patterson, 1995), it has an important drawback: it does not correct for regression towards the mean phenomenon. In an additional study (chapter 6) we investigated the impact of different correction methods and concluded that the regression-based QALY adjustment was the preferred correction method. If we calculate the ICERs using the regression-based QALY adjustment, this method showed more uncertainty about the study findings of the EE compared to calculation of the ICERs using the delta adjustment method. When using this correction method after bootstrapping, 98% of the ICERs were situated in the Southeast Quadrant compared to 63% using regression-based QALY adjustment. Can we therefore still say that the SSIC is a cost-effective treatment? Yes, because the point estimates indicate dominance of the SSIC treatment; there is, however, more uncertainty about this, as 33% of the ICERs lay in the Southwest quadrant, indicating

that the SSIC intervention is cost saving but not more effective compared to care as usual.

6 Summary of recommendations

Based on the evidence of this thesis we would recommend:

1. a before-after multicenter trial that evaluates the entire clinical pathway instead of a randomised controlled trial in a single center with the focus on an intervention that only evaluates the first eight hours of intensive care treatment as study design;
2. not only a CEA as analysis design, but also outcomes that are more relevant to the primary audience, like costs of implementation;
3. not only a hospital, but also a societal perspective;
4. to include both low and high-risk CABG patients instead of low-risk on a long-term follow-up (of one year) for all study outcomes instead of the one month follow-up for clinical outcomes and costs used in the SSIC study;
5. the SF-6D or EQ-5D for the measurement of generic QoL;
6. the SAQ or MacNew instead of the MILQ for the measurement of disease specific QoL;
7. the regression-based QALY adjustment method instead of the delta adjustment method, if baseline imbalances in utility occur.

In conclusion, all the above listed recommendations are important for future research of studies evaluating new treatments in CABG patients, the last recommendation, however, applies to cost-effectiveness analyses in general, too.

7 Practical recommendations for future research

In this last part some practical recommendations for future research will be given based on the experience of performing the SSIC study.

7.1 Information to healthcare professionals

- Organize a kick off meeting at the start of the study for all healthcare professionals.
- Keep the study protocol, summary of treatment protocol, and telephone list available and up-to-date at a central place.
- Inform all healthcare professionals once a month about study progress, and immediately about protocol changes. Do not forget to inform new employees.

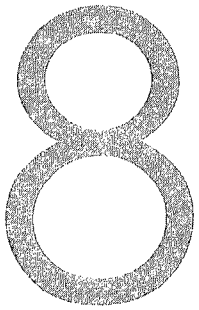
7.2 Treatment evaluation

- Perform multidisciplinary meetings once a week to evaluate the treatment of control and intervention patients. Record all main findings and issues.
- Give feedback on treatment issues and applications of case record forms to healthcare professionals as soon as possible.

7.3 Informed consent procedure and patient guidance

- Inform patients on the day of admission in the morning hours in an individual approach.
- Ask them to fill in questionnaires and let them write down questions concerning the study. Collect the questionnaires in the afternoon, and check missing items therefore.
- Visit patients frequently during hospital stay. Visit patients also at the day of discharge and inform them about their follow-up (e.g. questionnaires and hospital visits).

CHAPTER



Samenvatting

In dit hoofdstuk worden de belangrijkste bevindingen van dit proefschrift samengevat. In het eerste gedeelte van dit hoofdstuk wordt een samenvatting van de verschillende studies gegeven (1). De barrières voor implementatie van de short-stay intensive-care interventie worden besproken in het tweede gedeelte (2). In de laatste twee gedeeltes (3 en 4) wordt een samenvatting van de aanbevelingen voor verder onderzoek gegeven.

1 Samenvatting van de studies in het proefschrift

1.1 Huidige kennis met betrekking tot fast-track behandeling voor laagrisico CABG-patiënten (hoofdstuk 2)

In het tweede hoofdstuk van dit proefschrift worden de resultaten van een systematische literatuurstudie beschreven. 27 gerandomiseerde, gecontroleerde studies die fast-track behandelingen evalueerden werden gevonden in de MEDLINE en in de Cochrane databestanden. Omdat de verschillende studies heterogeen waren wat betreft de onderzochte interventies is een metaregressie analyse uitgevoerd. Hierbij zijn de studies ingedeeld op grond van belangrijke kenmerken van fast-track behandelingen: type en dosis anestheticum, extubatietijd en temperatuurmanagement. De belangrijkste bevinding van deze metaregressie analyse is dat de introductie van een protocol dat gericht is op snelle extubatie een belangrijke voorspeller is voor de afname van het totaal aantal uren intensive-care verblijf en ziekenhuisverblijf bij laagrisico CABG-patiënten.

In dit hoofdstuk zijn ook de verschillende studies onderzocht op hun methodologische kwaliteit. De epidemiologische kwaliteit van de 27 studies was redelijk. Eén studie voldeed aan alle drie methodologische criteria: het gebruik van intention-to-treat analyse voor de primaire studie uitkomst (intensive-care verblijf), allocation concealment (het geheim houden of blinderen van de toewijzing van patiënten aan de verschillende onderzoeksgroepen) en blindering van de personen die de lengte van

de intensive-care duur bepalen. De kwaliteit van de economische evaluaties van de studies is onderzocht aan de hand van de Consensus Health Economics Criteria list (CHEC-list). The CHEC-list scores van de 17 gescoorde items van de studies was laag (gemiddeld 8 punten). Dit was met name te wijten aan een verkeerde keuze van het onderzoeksdesign en verkeerd gebruik van methoden om de kosten te berekenen. De bevindingen van deze literatuurstudie laten zien dat er een noodzaak is om zowel de kwaliteit van de initiële studies alsmede die van de economische evaluaties te verbeteren.

1.2 Klinische effectiviteit en kosteneffectiviteit van het short-stay intensive care protocol (hoofdstuk 3)

Het effect van een short-stay intensive-care verblijf is onderzocht bij zeshonderd laagrisico CABG-patiënten door middel van een gerandomiseerde, gecontroleerde klinische equivalentie trial en een hieraan gekoppelde economische evaluatie. Patiënten die een laagrisico hadden op complicaties mochten meedoen in deze studie. Inclusie criteria waren bijvoorbeeld: jonger dan 78 jaar, een ejectiefractie van meer dan 30%, geen dialyse nodig hebben, geen pulmonaire hypertensie. De cardiologische toestand van de patiënten moest eveneens stabiel zijn. Patienten ingedeeld in de SSIC-groep werden binnen 8 uur overgeplaatst van de intensive care naar de medium care als ze voldeden aan de volgende ontslagcriteria: extubatie gedurende minstens 30 minuten, normale ademhaling, arteriële bloed gassen Pa_{O_2} > 10 kPa and Pa_{CO_2} < 6.0 kPa, cardiologisch stabiel, vochtbalans onder controle (≤ 100 ml thorax drain per uur en een diurese > 0.5 ml/kg/uur), geen signalen en symptomen van neurologische complicaties en geen noodzaak voor hemodynamische en ondersteunende therapie.
De primaire studie uitkomsten waren het aantal intensive-care heropnames en de totale duur van de ziekenhuisopname. Vier controlegroep patiënten (1.34%) en acht (2.68%) SSIC-patiënten werden heropgeno-

men op de intensive-care afdeling. Het verschil van 1.13% tussen beide groepen was niet significant verschillend (P-waarde = .241; 95% betrouwbaarheidsinterval: -.9% tot 2.9%). Er werd ook geen verschil gevonden in de twee groepen met betrekking tot de totale duur van de ziekenhuisopname en de andere secundaire uitkomsten postoperatieve morbiditeit en 30 dagen mortaliteit. De patiënten in de SSIC-groep verbleven significant minder uren op de intensive care vergeleken met de controlegroep patiënten. In de interventiegroep waren de totale kosten gemiddeld €816,- lager vergeleken met de gemiddelde kosten van de patiënten in de controlegroep. De kostenbesparing in de SSIC-groep werd voornamelijk veroorzaakt door lagere kosten van klinische verrichtingen en intensive- care verblijf. De kwaliteit van leven uitgedrukt in - delta van voor kwaliteit van leven gecorrigeerde levensmaanden (Δ QALM)- was significant verschillend tussen beide groepen, en hoger voor de SSIC-patiënten. De incrementele kosteneffectiviteitsratio en de 98% van de gebootstrapte ICERs lagen in het zuidwest-kwadrant. Dit geeft aan dat de SSIC-interventie dominant is ten opzichte van de standaard zorg. De conclusie van deze studie is dat de SSIC een veilige en kosteneffectieve behandeling is vergeleken met de huidige standaard behandeling (24-uur intensive-care zorg).

1.3 Kwaliteit van leven na een fast-track behandeling (hoofdstuk 4)

Het doel van deze gerandomiseerde, gecontroleerde equivalentie studie was het evalueren van ziekte specifieke, algemene en domein specifieke kwaliteit van leven tot een jaar na de short-stay intensive-care behandeling. Ziekte specifieke kwaliteit van leven werd gemeten met behulp van de Multidimensional Index of Life Quality, de algemene kwaliteit van leven door middel van de EQ-5D en de domein specifieke door middel van de Beck Depression Inventory en State-Trait Anxiety Inventory. De metingen werden verricht op de dag vóór de operatie en op één en twaalf maanden erna. De belangrijkste bevindingen van deze

studie zijn dat na een multivariate analyse op één jaar na de operatie geen significant verschil in kwaliteit van leven tussen SSIC-patiënten en controlegroep patiënten waar te nemen is. Ook na de correctie van mogelijke verstorende factoren (zoals bijvoorbeeld co-morbiditeiten en leeftijd) was er op één jaar na de operatie geen statistisch significant verschil tussen beide groepen waargenomen. De conclusie van deze studie is dat op het gebied van de kwaliteit van leven geen van de waargenomen verschillen tussen beide behandelingsgroepen klinisch relevant verschillend zijn.

1.4 Het testen van de validiteit en de betrouwbaarheid van de EuroQoL en Multidimensional Index of Life Quality (hoofdstuk 5)

Het doel van deze prospectieve studie was het testen van de validiteit en de betrouwbaarheid van de EuroQoL (EQ-5D) en de Multidimensional Index of Life Quality (MILQ) in CABG-patiënten.

De belangrijkste bevindingen van deze studie waren dat de discriminatieve validiteit in de vijf EQ-5D dimensies werd beperkt door plafondeffecten (het percentage patiënten met een maximale score). Deze effecten traden ook op bij twee van de negen MILQ-domeinen. De predictieve validiteit op één maand na de operatie van het EQ-5D domein angst/depressie, EQ-5D VAS, MILQ-domein fysieke gezondheid en de MILQ-score waren redelijk. Op 12 maanden na de operatie hadden de EQ-5D VAS, de MILQ-score en de twee fysieke dimensies van de MILQ een goede predictieve validiteit. Alleen het EQ-5D domein dagelijkse activiteiten en de EQ-5D VAS kunnen onderscheid maken tussen patiënten ingedeeld in de verschillende New York Heart Association functional classification categorieën (externe criterium validiteit). De test-hertest betrouwbaarheid van beide vragenlijsten kan worden geclassificeerd als onvoldoende.

De conclusies van deze studie zijn dat de discriminatieve validiteit van de EQ-5D domeinen, de externe criterium validiteit en de predictieve

validiteit van zowel de EQ-5D en de MILQ beperkt zijn. Daarnaast is de betrouwbaarheid van beide vragenlijsten niet toereikend. Op basis van de bevindingen van onze studie kunnen we concluderen dat beide vragenlijsten niet de voorkeur hebben bij het evalueren van de kwaliteit van leven van CABG-patiënten.

1.5 Correctiemethoden voor baseline utiliteitsverschillen tussen twee behandelingsstrategieën in voor kwaliteit van leven gecorrigeerde levensjaar berekeningen (hoofdstuk 6)

Het doel van deze laatste studie was het evalueren van verschillende strategieën die kunnen corrigeren voor baseline utiliteit verschillen in voor kwaliteit van leven gecorrigeerde levensjaar (QALY) berekeningen zodat er analyses kunnen worden gedaan op patiëntniveau.
De data van de trial die de short-stay intensive-care behandeling voor CABG-patiënten onderzocht, werd gebruikt als case studie. Vijf verschillende methoden werden toegepast: 1) de conventionele QALY berekening, waarbij geen baseline correctie plaatsvindt; 2) Correctie met de verschillen tussen de gemiddelde baseline utiliteit van beide behandelingsgroepen; 3) De Delta correctiemethode, waarbij alleen de veranderingen in de utiliteit tussen beide metingen wordt gebruikt; 4) een op regressie gebaseerde utiliteitscorrectie, waarbij een regressie-model wordt gebruikt met daarin de follow-up utiliteit als de afhankelijke variabele en de baseline utiliteit als de onafhankelijke variabele; 5) een op regressie gebaseerde QALY correctie, waarbij de QALY de afhankelijke en de baseline utiliteit de onafhankelijke variabele is in het regressiemodel.
De resultaten van deze studie laten zien dat het niet-gebruiken van een correctiemethode wanneer er wel baseline utiliteitsverschillen optreden, resulteert in verschillende kosteneffectiviteit uitkomsten. De mate van de invloed van de correctiemethoden is afhankelijk van welk type correctiemethode er wordt gebruikt. Op basis van de resultaten van deze studie wordt aanbevolen dat wanneer er een baseline verschil in de utiliteit

wordt waargenomen deze het beste kan worden gecorrigeerd met behulp van de regressie-gebaseerde QALY correctie. De uitkomsten van de andere correctiemethoden kunnen worden gerapporteerd in aanvullende sensitiviteitsanalyses.

2 Mogelijkheden voor implementatie van het huidige short-stay intensive care protocol

De bevindingen van de SSIC-studie laten zien dat de resultaten aanleiding zouden kunnen zijn om het SSIC-protocol te implementeren in de Nederlandse ziekenhuizen. Echter meer dan drie jaar na de publicatie van de belangrijkste bevindingen van de SSIC-studie hebben we echter geen informatie dat ziekenhuizen op dit moment het SSIC- protocol gebruiken.

De redenen waarom dit tot op heden nog niet gebeurd is, worden uitgebreid besproken in hoofdstuk 7, paragraaf 2. Een van de redenen die kan worden geopperd, is dat de implementatie op basis van één onderzoek niet voldoende reden is voor beleidsmakers om volgens het SSIC-protocol te gaan werken. Daarnaast zijn er een heel aantal potentiële barrières te bedenken die implementatie van het SSIC-protocol in de huidige vorm in de weg kunnen staan. Zoals de infrastructuur van de verschillende intensive en medium care afdelingen in de diverse cardiothorale centra in Nederland. Als bijvoorbeeld CABG-patiënten op gemengde IC's liggen, heeft dit direct gevolgen voor de patiëntenlogistiek. Een ander voorbeeld van een barrière kan zijn dat er hoge kosten moeten worden gemaakt voor het verbouwen van de IC en MC afdelingen als er geen apparte MC aanwezig is. Een belangrijke andere barrière is dat het met het huidige protocol niet mogelijk is om exact te bepalen hoeveel patiënten wanneer op welke afdeling liggen, waardoor het moeilijk is om een personeelsplanning te maken. Daarnaast is het zo dat door recente veranderingen in de patiëntenpopulatie er minder laagri-

sico CABG-patiënten zijn, waardoor het implementeren van een protocol specifiek voor deze groep geen hoge prioriteit heeft.

3 Samenvatting van de aanbevelingen

Gebaseerd op de bevindingen van dit proefschrift kunnen de volgende aanbevelingen worden gedaan:

1. gebruik een vóór-na trial die de totale behandeling van CABG-patiënten evalueert in verschillende ziekenhuizen in plaats van een gerandomiseerde, gecontroleerde trial die alleen de eerste 8 uur intensive-care behandeling in één ziekenhuis evalueert;
2. neem naast de klinische en kosteneffectiviteit ook uitkomsten mee die relevant zijn voor het primaire publiek van de studie (managers van de IC's en directie van ziekenhuizen), zoals de kosten van implementatie en scenario analyses die de impact van een nieuwe behandeling op veranderingen van patiëntstromen en wachtlijsten inzichtelijk maken;
3. neem een maatschappelijk en ziekenhuis perspectief als uitgangspunt voor de economische evaluatie in plaats van alleen een ziekenhuis perspectief;
4. meet alle studieuitkomsten bij zowel hoog- als laagrisico CABG-patiënten met een lange termijn follow-up (1 jaar) in plaats van alleen laagrisico en een korte termijn follow-up voor klinische effecten en kosten zoals in de SSIC-studie;
5. gebruik de SF-6D of de EQ-5D voor het meten van algemene kwaliteit van leven;
6. gebruik de Seatlle Angina of MacNew vragenlijst in plaats van de MILQ voor de meting van ziekte specifieke kwaliteit van leven;

7. gebruik, als er baseline verschillen in utilitieitsmetingen optreden, de op QALY gebaseerde regressie correctiemethode voor de berekening van voor kwaliteit van leven gecorrigeerde levensjaren in plaats van de delta correctiemethode.

Samenvattend: alle aanbevelingen die hierboven zijn opgenoemd zijn belangrijk voor toekomstig onderzoek die nieuwe behandelingen voor CABG-patiënten evalueren. De laatste aanbeveling is echter ook van belang voor kosteneffectiviteitsanalyses in het algemeen.

4 Praktische aanbevelingen voor toekomstig onderzoek

In dit laatste gedeelte wordt een aantal praktische aanbevelingen gedaan voor toekomstig onderzoek.

4.1 Informatie voor personeel in de gezondheidszorg

- Organiseer een kick-off meeting aan het begin van de studie voor al het betrokken personeel.
- Houd het onderzoeksprotocol, een samenvatting van het behandelingsprotocol en een up-to-date telefoonlijst beschikbaar op een centrale plaats.
- Informeer al het personeel eens per maand over de studie voortgang, en onmiddellijk over wijzigingen in het protocol. Vergeet niet nieuwe medewerkers te informeren.

4.2 Evaluatie van de behandeling

- Houd wekelijks multidisciplinaire meetings en evalueer de behandeling van zowel interventie- alsook controlegroep patiënten. Notuleer alle belangrijke bevindingen en onderwerpen.

- Geef zo snel als mogelijk feedback aan het personeel over behandelingsgerelateerde onderwerpen en het invullen van Case Record Forms.

4.3 Informed consent procedure en patiëntenbegeleiding

- Informeer patiënten persoonlijk op de dag van de opname, in de ochtend.
- Vraag of ze de vragenlijsten willen invullen en vragen te noteren. Verzamel de vragenlijsten in de namiddag en controleer op eventueel onbrekende items.
- Bezoek de patiënten regelmatig gedurende hun verblijf in het ziekenhuis. Bezoek hen ook op de dag dat ze naar huis gaan en informeer ze dan over de follow-up (bijvoorbeeld vragenlijsten en poliklinische bezoeken).